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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,931	10/11/2005	Myra Gilligan	T1629YP	6852

210 7590 03/31/2008
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EXAMINER	
O'DELL, DAVID K	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
03/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,931	GILLIGAN ET AL.	
	Examiner	Art Unit	
	David K. O'Dell	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20 and 22-26* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

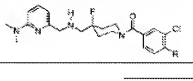
1. Claims 20-26 are pending in the current application.

2. This application is a 371 of PCT/GB04/01998 filed 05/07/2004, which claims priority to Great Britain application 0311349.5 filed 05/16/2003.

Response to Arguments

3. Applicant's arguments filed on January 14, 2008 have been fully considered but they are not fully persuasive. The objection at least for what was claim 15, now claim 25, is withdrawn since a minor spelling error was corrected. The claim 21 is objected for depending from a rejected base claim but is otherwise allowable. However, with respect to the rejection under 35 U.S.C. 103 (a) for obviousness, the rejection of the remaining claims is maintained for the reasons of record in so far as these compounds are bioisosteric replacements of hydrogen with fluorine atom. The examiner agrees with the applicant that these compounds are really not position isomers, but maintains that they are best viewed as bioisosteres of the prior art compound. This is a very straightforward and viable rejection. The applicant has argued that the examiners bioisosterism analysis is deficient in the sense that this precise 4-fluoropiperidine would not have been arrived at from the teaching of the prior art. The examiner disagrees and submits that 4-fluoropiperidines are conventional and even highly desirable structural motifs in 5-HT receptor art, and so as not to be accused of taking official notice the examiner submits that Vacher et. al. "Novel Derivatives of 2-Pyridinemethylamine as Selective, Potent, and Orally Active Agonists at 5-HT1A Receptors" *Journal of Medicinal Chemistry* **1999**, *42*, 1648 – 1660, teaches these precise 4-fluoro piperidines, See Tables 4 and 5 below:

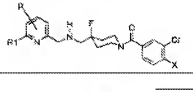
Table 4. Effect of the Nature of the Para Substituent on Receptor Affinity Profile and on 5-HT_{1A} Agonist Activity in Vitro (cAMP) and in Vivo (LLR)



						5-HT_{1A} agonist activity		
						ED_{50} (mg/kg)[a] to produce LLR[f]		
		receptor affinity (pKi)[b,c]				i.p.		p.o.
compd	R	5-HT_{1A}	D_2	α_1	cAMP[d] pEC_{50}	15 min	60 min	60 min
43	H	10.01 (0.04)	6.21 (0.04)	6.81 (0.05)	8.00 (0.45)	0.08	0.11	0.32
44	CH_3	9.57 (0.05)	6.89 (0.15)	6.86 (0.06)	8.24 (0.22)	0.08	0.08	0.32
45	F	9.92 (0.05)	6.56 (0.06)	6.88 (0.09)	8.14 (0.09)	0.29	0.11	0.16
46	Cl	9.61 (0.07)	6.48 (0.22)	6.76 (0.04)	8.53 (0.09)	0.62	0.45	0.32

[a-c] See footnotes of Table 2. [d] ED_{50} values were obtained by linear interpolation. [f] LLR = lower lip retraction.

Table 5. 5-Unsubstituted and -Substituted Derivatives: Comparisons of Their Affinity and Agonist Activity at 5-HT_{1A} Receptors in Vitro (cAMP) and in Vivo (LLR)

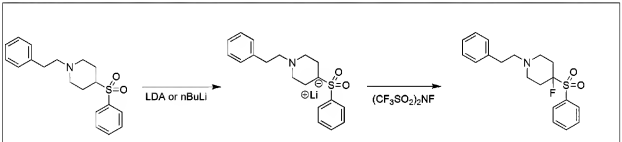


						5-HT_{1A} agonist activity	
						LLR. ED_{50} (mg/kg)[a]	
compd	R	R_1	X	receptor affinity 5-HT_{1A} pK_i[a,b]	cAMP[d] pEC_{50}	i.p. (15 min)	p.o. (60 min)
34	5-CH_3	H	Cl	9.24 (0.07)	7.68 (0.12)	NT	0.62
35	5-CH_3	H	F	9.07 (0.05)	7.59 (0.04)	0.08	0.11
36	5-CH_2CH_3	H	F	8.05 (0.10)	6.39 (0.25)	1.90	1.90
37	5-$CH(CH_3)_2$	H	F	7.45 (0.05)	NT	NT	NT
38	H	CH_3NH	F	9.69 (0.05)	7.90 (0.39)	0.11	0.32
40	5-CH_3	CH_3NH	F	10.12 (0.11)	8.67 (0.02)	0.02	0.08
41	H	CH_3CH_2NH	F	9.73 (0.09)	7.88 (0.62)	0.11	0.32
42	5-CH_3	CH_3CH_2NH	F	9.83 (0.01)	8.08 (0.24)	0.08	0.45
48	H	$(CH_3)_2N$	F	9.92 (0.09)	8.44 (0.05)	0.29	0.16
47	5-CH_3	$(CH_3)_2N$	F	9.33 (0.08)	7.32 (0.12)	0.63	1.30
48	4-CH_3	$(CH_3)_2N$	F	9.25 (0.03)	7.48 (0.09)	0.32	0.89
49	5-CH_3	$(CH_3)_2N$	F	9.50 (0.09)	8.43 (0.15)	0.04	0.08
50	H	$(CH_3CH_2)_2N$	F	8.94 (0.01)	7.89 (0.10)	0.11	1.0
51	5-CH_3	$(CH_3CH_2)_2N$	F	9.86 (0.07)	7.54 (0.09)	0.32	0.11
59	H	pyrazol-1-yl	F	9.31 (0.06)	7.91 (0.04)	0.32	1.30
60	5-CH_3	pyrazol-1-yl	F	9.35 (0.08)	7.83 (0.09)	0.32	1.30
62	H	pyrazol-3-yl	F	9.04 (0.12)	8.14 (0.19)	0.32	0.32
63	5-CH_3	pyrazol-3-yl	F	8.68 (0.04)	8.56 (0.01)	0.32	0.89

[a-d] See footnotes of Table 2. [e] LLR = lower lip retraction; ED_{50} values were obtained by linear interpolation.

In fact this teaching reveals F13640, which is a very well known compound in this area and contains the 4-fluoropiperidine motif. The other main thrust of the applicant's arguments seem to be that even if one were to arrive at the instant compounds from the prior art teaching it would not occur to a chemist of ordinary skill how to make them. The examiner respectfully disagrees, and submits that even the examiner, who is one of less than ordinary skill in the art, recognizes that the instantly claimed compounds can be prepared from the prior art compounds. The proton

α to the sulfonyl group (i.e. the 4-piperidine CH) is reasonably acidic and should readily deprotonate upon treatment with an organolithium or other base. The subsequent anions would easily react with electrophilic fluorinating agents that are known in the art like $(CF_3SO_2)_2NF$ (Lal et. al. "Electrophilic NF Fluorinating Agents" *Chemical Reviews* **1996**, *96*, 1737-1755. Section B 1b pg. 1746-1747 in particular.) This straightforward route is illustrated graphically in Scheme 1.



Scheme 1. A proposed fluorination of the prior art compounds.

In addition the prior art compounds in a large measure are polyfluorinated and this seems to suggest that further fluorination would be desirable. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This action is FINAL.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 20, 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fletcher, S. R. et. al. "4-(Phenylsulfonyl)piperidines: Novel, Selective, and Bioavailable 5-HT2A Receptor Antagonists." *Journal of Medicinal Chemistry*, **2002**, *45*, 492-503 (cited on IDS) AND Ackermann et. al. WO 2001/51469 (cited on IDS) AND Blurton, et. al. WO 2000/043362 (cited on IDS) AND Wang, H. et. al. "Synthesis and biological activities of new 5-HT2A selective ligands N-substituted-piperidinyl-4-phenylthioether and sulfone derivatives." *Yaoxue Xuebao*, **2001**, *36*, 274-277, (abstract only), in view of Patani et. al. "Bioisosterism: A Rational Approach in Drug Design" *Chemical Reviews* **1996**, *96*, 3147-3176. The claims are drawn to compounds where Ar is phenyl, n is 1 or 0, m is 0 or 1 and W is (C=O) or CH2, with the various Q and R1-R4 definitions as below in the fifty or so compounds of Ackermann, Blurton, Fletcher, and Wang. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

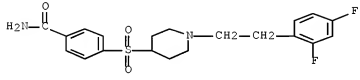
Determination of the scope and content of the prior art

(MPEP 2141.01)

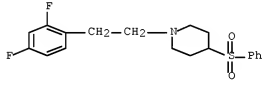
Fletcher, Ackerman, Blurton, and Wang et. al. teach compounds that are bioisosteric replacements of hydrogen atom with fluorine atom. These compounds have the same activity namely at the 5HT2a receptor.

In particular Fletcher teaches the following compounds:

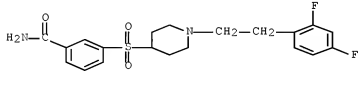
RN 285994-74-3 CAPLUS
CN Benzamide, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
(9CI) (CA INDEX NAME)



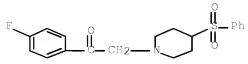
RN 285994-92-5 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-(phenylsulfonyl)- (9CI)
(CA
INDEX NAME)



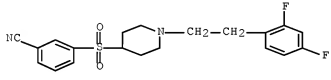
RN 285994-94-7 CAPLUS
CN Benzamide, 3-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
(9CI) (CA INDEX NAME)



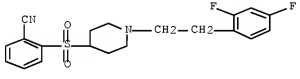
RN 285994-99-2 CAPLUS
CN Ethanone, 1-(4-fluorophenyl)-2-[4-(phenylsulfonyl)-1-piperidinyl]- (9CI)
(CA INDEX NAME)



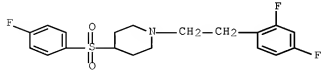
RN 400729-07-9 CAPLUS
CN Benzonitrile, 3-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
(9CI) (CA INDEX NAME)



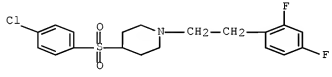
RN 400729-08-0 CAPLUS
CN Benzonitrile, 2-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
(9CI) (CA INDEX NAME)



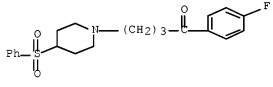
RN 400729-09-1 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[(4-fluorophenyl)sulfonyl]-
(9CI) (CA INDEX NAME)



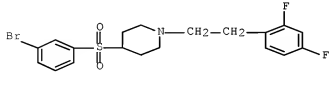
RN 400729-10-4 CAPLUS
CN Piperidine, 4-[(4-chlorophenyl)sulfonyl]-1-[2-(2,4-difluorophenyl)ethyl]-
(9CI) (CA INDEX NAME)



RN 400729-13-7 CAPLUS
CN 1-Butanone, 1-(4-fluorophenyl)-4-[4-(phenylsulfonyl)-1-piperidinyl]-
(9CI)
(CA INDEX NAME)

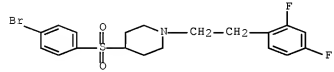


IT 285995-09-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and structure activity of 4-(phenylsulfonyl)piperidines
as
novel, selective, and bioavailable 5-HT2A receptor antagonists)
RN 285995-09-7 CAPLUS
CN Piperidine, 4-[(3-bromophenyl)sulfonyl]-1-[2-(2,4-difluorophenyl)ethyl]-
(9CI) (CA INDEX NAME)

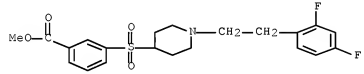


IT 285995-02-0P 285995-10-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT

(Reactant or reagent)
(preparation and structure activity of 4-(phenylsulfonyl)piperidines as
novel, selective, and bioavailable 5-HT2A receptor antagonists)
RN 285995-02-0 CAPLUS
CN Piperidine, 4-[(4-bromophenyl)sulfonyl]-1-[2-(2,4-difluorophenyl)ethyl]-
(9CI) (CA INDEX NAME)

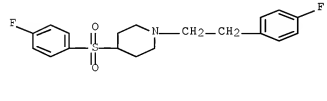


RN 285995-10-0 CAPLUS
CN Benzoic acid, 3-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
, methyl ester (9CI) (CA INDEX NAME)

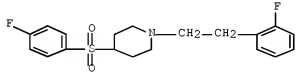


Ackermann et. al. teaches more of the same compounds:

RN 349664-80-8 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(4-fluorophenyl)sulfonyl]-,
hydrochloride (9CI) (CA INDEX NAME)

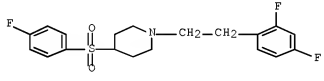


RN 349664-81-9 CAPLUS
CN Piperidine, 1-[2-(2-fluorophenyl)ethyl]-4-[(4-fluorophenyl)sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



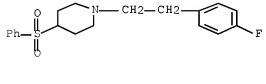
● HCl

RN 349664-82-0 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[(4-fluorophenyl)sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



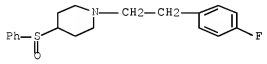
● HCl

RN 349664-83-1 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-(phenylsulfonyl)-, hydrochloride (9CI) (CA INDEX NAME)



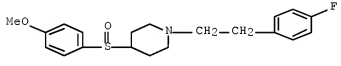
● HCl

RN 349664-84-2 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-(phenylsulfinyl)-, hydrochloride
(9CI) (CA INDEX NAME)



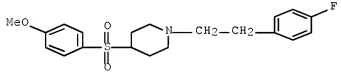
● HCl

RN 349664-87-5 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(4-methoxyphenyl)sulfinyl]-, hydrochloride (9CI) (CA INDEX NAME)



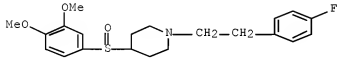
● HCl

RN 349664-88-6 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(4-methoxyphenyl)sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



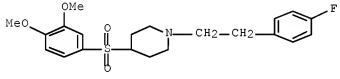
● HCl

RN 349664-89-7 CAPLUS
CN Piperidine, 4-[(3,4-dimethoxyphenyl)sulfinyl]-1-[2-(4-fluorophenyl)ethyl]-
, hydrochloride (9CI) (CA INDEX NAME)



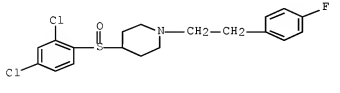
● HCl

RN 349664-90-0 CAPLUS
CN Piperidine, 4-[(3,4-dimethoxyphenyl)sulfonyl]-1-[2-(4-fluorophenyl)ethyl]-
, hydrochloride (9CI) (CA INDEX NAME)



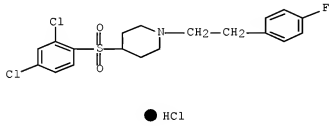
● HCl

RN 349664-91-1 CAPLUS
CN Piperidine, 4-[(2,4-dichlorophenyl)sulfinyl]-1-[2-(4-fluorophenyl)ethyl]-,
hydrochloride (9CI) (CA INDEX NAME)

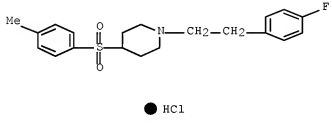


● HCl

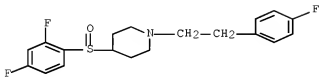
RN 349664-92-2 CAPLUS
CN Piperidine, 4-[(2,4-dichlorophenyl)sulfonyl]-1-[2-(4-fluorophenyl)ethyl]-,
hydrochloride (9CI) (CA INDEX NAME)



RN 349664-94-4 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(4-methylphenyl)sulfonyl]-,
hydrochloride (9CI) (CA INDEX NAME)

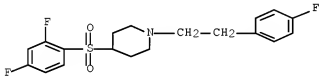


RN 349664-95-5 CAPLUS
CN Piperidine, 4-[(2,4-difluorophenyl)sulfinyl]-1-[2-(4-fluorophenyl)ethyl]-,
hydrochloride (9CI) (CA INDEX NAME)



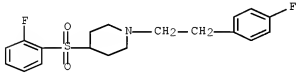
● HCl

RN 349664-96-6 CAPLUS
CN Piperidine, 4-[(2,4-difluorophenyl)sulfonyl]-1-[2-(4-fluorophenyl)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)



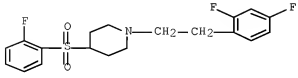
● HCl

RN 349664-97-7 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(2-fluorophenyl)sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



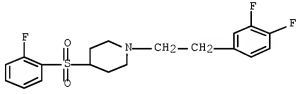
● HCl

RN 349664-98-8 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[(2-fluorophenyl)sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



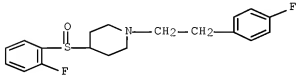
● HCl

RN 349664-99-9 CAPLUS
CN Piperidine, 1-[2-(3,4-difluorophenyl)ethyl]-4-[(2-fluorophenyl)sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

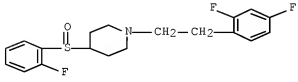
RN 349665-03-8 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(2-fluorophenyl)sulfinyl]-, hydrochloride (9CI) (CA INDEX NAME)



● HCl

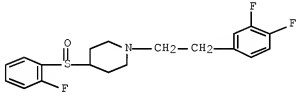
RN 349665-04-9 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[(2-fluorophenyl)sulfinyl]-,

hydrochloride (9CI) (CA INDEX NAME)



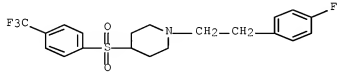
● HCl

RN 349665-05-0 CAPLUS
CN Piperidine, 1-[2-(3,4-difluorophenyl)ethyl]-4-[(2-fluorophenyl)sulfinyl]-,
hydrochloride (9CI) (CA INDEX NAME)



● HCl

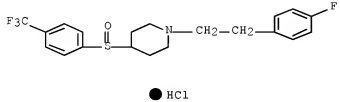
RN 349665-06-1 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[[4-(trifluoromethyl)phenyl]sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)



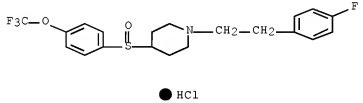
● HCl

RN 349665-07-2 CAPLUS

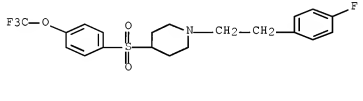
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[[4-(trifluoromethyl)phenyl]sulfinyl]-, hydrochloride (9CI) (CA INDEX NAME)



RN 349665-08-3 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[[4-(trifluoromethoxy)phenyl]sulfinyl]-, hydrochloride (9CI) (CA INDEX NAME)

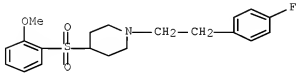


RN 349665-09-4 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[[4-(trifluoromethoxy)phenyl]sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)

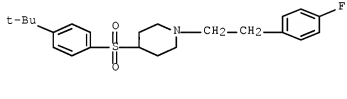


RN 349665-10-7 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[(2-methoxyphenyl)sulfonyl]-,

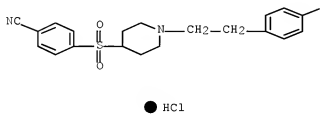
hydrochloride (9CI) (CA INDEX NAME)



RN 349665-12-9 CAPLUS
CN Piperidine, 4-[[4-(1,1-dimethylethyl)phenyl]sulfonyl]-1-[2-(4-fluorophenyl)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

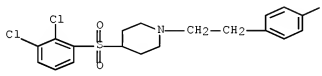


RN 349665-14-1 CAPLUS
CN Benzonitrile, 4-[[1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-, monohydrochloride (9CI) (CA INDEX NAME)



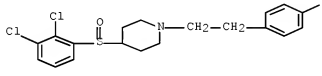
RN 349665-17-4 CAPLUS

CN Piperidine, 4-[(2,3-dichlorophenyl)sulfonyl]-1-[2-(4-fluorophenyl)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)



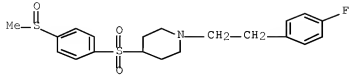
● HCl

RN 349665-18-5 CAPLUS
CN Piperidine, 4-[(2,3-dichlorophenyl)sulfinyl]-1-[2-(4-fluorophenyl)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

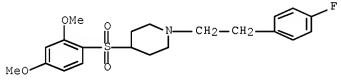


● HCl

RN 349665-25-4 CAPLUS
CN Piperidine, 1-[2-(4-fluorophenyl)ethyl]-4-[[4-(methylsulfinyl)phenyl]sulfonyl]-, hydrochloride (9CI) (CA INDEX NAME)

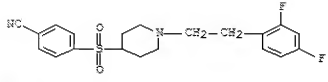


RN 349665-29-8 CAPLUS
CN Piperidine, 4-[(2,4-dimethoxyphenyl)sulfonyl]-1-[2-(4-fluorophenyl)ethyl]-
, hydrochloride (9CI) (CA INDEX NAME)

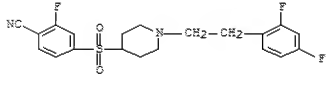


Blurton, et. al. WO 2000/043362 teaches the following compounds:

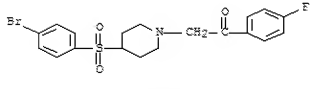
RN 285994-62-9 CAPLUS
CN Benzonitrile, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
(9CI) (CA INDEX NAME)



RN 285994-66-3 CAPLUS
CN Benzonitrile, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-
2-fluoro- (9CI) (CA INDEX NAME)



RN 285994-96-9 CAPLUS
CN Ethanone, 2-[4-[(4-bromophenyl)sulfonyl]-1-piperidinyl]-1-(4-fluorophenyl)-
(9CI) (CA INDEX NAME)

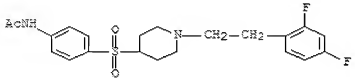


IT 285994-54-1P 285994-58-5P 285994-70-9P

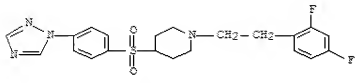
(Prepn. of phenylsulfonyl derivs. as 5-HT receptor ligands)

RN 285994-64-1 CAPLUS

CN Acetamide, N-[4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]phenyl]- (9CI) (CA INDEX NAME)

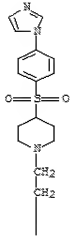


RN 285994-68-5 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



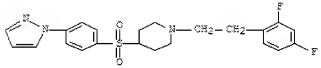
RN 285994-70-9 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(1H-imidazol-1-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

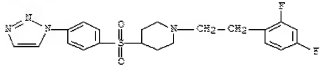


PAGE 2-A

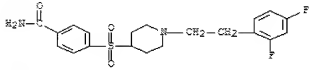
RN 285994-72-1 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(1H-pyrazol-1-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



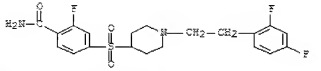
RN 285994-73-2 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



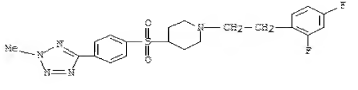
RN 285994-74-3 CAPLUS
CN Benzamide, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



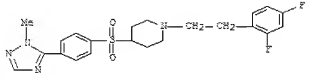
RN 285994-76-5 CAPLUS
CN Benzamide, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-2-fluoro- (9CI) (CA INDEX NAME)



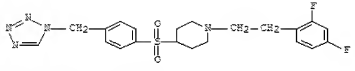
RN 285994-78-7 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(2-methyl-2H-tetrazol-5-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



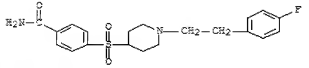
RN 265994-80-1 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(1-methyl-1H-1,2,4-triazol-5-yl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



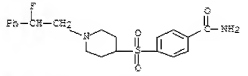
RN 265994-82-3 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-[[4-(2H-tetrazol-1-ylmethyl)phenyl]sulfonyl]- (9CI) (CA INDEX NAME)



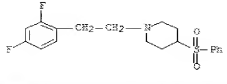
RN 265994-86-7 CAPLUS
CN Benzamide, 4-[[1-[2-(4-fluorophenyl)ethyl]-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



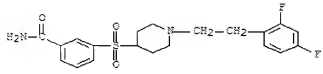
RN 265994-90-2 CAPLUS
CN Benzamide, 4-[[1-(2-fluoro-2-phenylethyl)-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



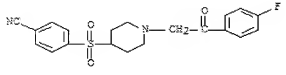
RN 265994-92-4 CAPLUS
CN Piperidine, 1-[2-(2,4-difluorophenyl)ethyl]-4-(phenylsulfonyl)- (9CI) (CA INDEX NAME)



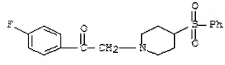
RN 285994-94-7 CAPLUS
CN Benzamide, 3-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



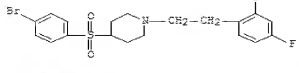
RN 285994-98-1 CAPLUS
CN Benzonitrile, 4-[[1-[2-(4-fluorophenyl)-2-oxoethyl]-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 285994-99-2 CAPLUS
CN Ethanone, 1-(4-fluorophenyl)-2-[4-(phenylsulfonyl)-1-piperidinyl]- (9CI) (CA INDEX NAME)

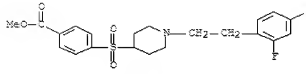


IT 285995-02-0P 285995-03-1P 285995-04-2P
285995-07-5P 285995-08-6P 285995-09-7P
285995-10-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of phenylsulfonyl derivs. as 5-HT receptor ligands)
RN 285995-02-0 CAPLUS
CN Piperidine, 4-[(4-bromophenyl)sulfonyl]-1-[2-(2,4-difluorophenyl)ethyl]- (9CI) (CA INDEX NAME)

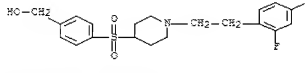


RN 285995-05-1 CAPLUS
CN Benzoic acid, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

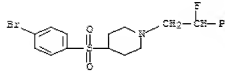
RN 285995-03-1 CAPLUS
CN Benzoic acid, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)



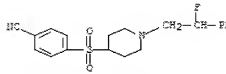
RN 285995-04-2 CAPLUS
CN Benzenemethanol, 4-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



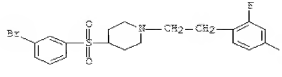
RN 285995-07-5 CAPLUS
CN Piperidine, 4-[(4-bromophenyl)sulfonyl]-1-(2-fluoro-2-phenylethyl)- (9CI) (CA INDEX NAME)



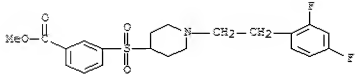
RN 285995-08-6 CAPLUS
CN Benzonitrile, 4-[[1-(2-fluoro-2-phenylethyl)-4-piperidinyl]sulfonyl]- (9CI) (CA INDEX NAME)



RN 285995-09-7 CAPLUS
CN Piperidine, 4-[(3-bromophenyl)sulfonyl]-1-[2-(2,4-difluorophenyl)ethyl]- (9CI) (CA INDEX NAME)

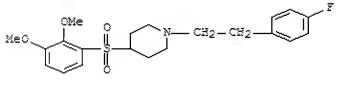


RN 255995-10-0 CAPLUS
CN Benzoic acid, 3-[[1-[2-(2,4-difluorophenyl)ethyl]-4-piperidinyl]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

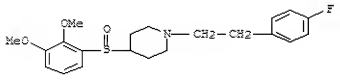


Wang teaches the following compounds:

RN 403848-68-0 CAPLUS
CN Piperidine, 4-[(2,3-dimethoxyphenyl)sulfonyl]-1-[2-(4-fluorophenyl)ethyl]- (9CI) (CA INDEX NAME)



RN 403848-70-4 CAPLUS
CN Piperidine, 4-[(2,3-dimethoxyphenyl)sulfinyl]-1-[2-(4-fluorophenyl)ethyl]- (9CI) (CA INDEX NAME)



Patani teaches that the exact bioisosteric replacement seen here (H to F) is well known and the art:

> **"II. Classical Bioisosteres A. Monovalent Atoms or Groups**
> Similarities in certain physicochemical properties have enabled investigators to successfully exploit several monovalent bioisosteres. These can be divided into the following groups: (1) fluorine vs hydrogen replacements; (2) amino-hydroxyl interchanges; (3) thiol-hydroxyl interchanges; (4) fluorine, hydroxyl, amino, and methyl group interchanges (Grimm's Hydride

Displacement Law); (5) chloro, bromo, thiol, and hydroxyl group interchanges (Erlenmeyer's Broadened Classification of Grimm's Displacement Law).
1. Fluorine vs Hydrogen Replacements
The substitution of hydrogen by fluorine is one of the more commonly employed monovalent isosteric replacements." Patani et. al. pg. 3149.

Ascertainment of the difference between the prior art and the claims

It is clear that the prior compounds differ only from the compounds of the instant case by the replacement of a hydrogen with a fluorine.

Finding of prima facie obviousness

Rational and Motivation
(MPEP 2142-2143)

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare position isomers or bioisosteres of those of Ackermann, Blurton, Fletcher, or Wang to produce the instant invention. Positional isomers, having the same radical on different positions of the molecule, are *prima facie* obvious, and require no secondary teaching. The experienced Ph.D. synthetic organic chemist, who would make Applicants' compounds, would be motivated to prepare these analogs based on the expectation that such close analogues would have similar properties and upon the routine nature of such experimentation in the art of medicinal chemistry. Indeed it is clear that these compounds have exactly the same properties as those of Ackermann, Blurton, Fletcher, or Wang, namely activity at the 5-HT2a receptor. It would be routine for the chemist to vary the point of attachment in order to increase potency and to establish better patent protection for her compounds.

The bioisosteric replacement of H with F, was well known at the time the invention was made as evidience by Patani et. al. Moreover by looking at the structure of the compounds of Ackermann, Blurton, and Fletcher in particular it is clear that polyfluorinated compounds were the preferred compounds of these inventions. *Ex parte Engelhardt*, 208 USPQ 343 at 349, "[i]f functional groups capable of withdrawing or repelling electrons are located in the chain or ring (emphasis added) of a biologically active compound, transfer of such groups to other positions in

which their electronic effects are lessened or enhanced may alter the biological activity of the modified compound.", *In re Grabiak* 226 USPQ 870, "[w]hen chemical compounds have "very close" structural similarities and similar utilities, without more a *prima facie* case may be made", *Ex parte Dole* 119 USPQ 260, where a tetrachloro compound was held unpatentably obvious over the dichloro analog, shown in Figure 1.

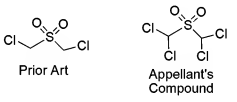


Figure 1. Structures of Ex Parte Dole.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

One of ordinary skill is also one of "ordinary creativity, not an automaton". See Leapfrog Enterprises Inc. v. Fisher-Price. and Mattel Inc. UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT "An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at 12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Objections

5. Claim 21 is drawn to compounds where the Ar ring is either bezisothiazolyl-3-yl or benzothiophenyl-3-yl and is objected to for depending from a rejected base claim, but would be allowable if put in proper dependent format.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Primary examiner, Rita Desai can be reached on (571)272-0684. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625